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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville MD 20857

August 3, 1995

Vincent De Stefano
Manager, Regulatory Affairs
Ciba Self-Medication, Inc.
Mack Woodbridge II
581 Main Street
Woodbridge, New Jersey 07095

Re: Docket No. 78N-036L
Comment No. C161

Dear Mr. De Stefano:

This letter concerns your August 30, 1994 request that the tentative final monograph for over-the-counter (OTC) laxative drug products be amended to include the combination of bisacodyl and docusate sodium (DSS). This request was made in response to the notice of proposed rulemaking published in the FEDERAL REGISTER of September 2, 1993 (58 FR 46589). Your August 30, 1994 request was filed as Comment No. C161 under Docket No. 78N-036L in FDA's Dockets Management Branch on July 5, 1995.

You requested monograph status for the combination of bisacodyl and DSS for the following reasons: (1) Each ingredient was proposed as Category I (safe and effective) in the tentative final monograph; (2) the proposed bisacodyl/DSS combination meets the criteria for Category I combinations set forth in the advance notice of proposed rulemaking for OTC laxative drug products (40 FR 12921); and (3) the additional data provided support the combination. In addition, you mentioned that phenolphthalein has a chemical structure that is similar to bisacodyl. Therefore, one would not expect a difference in the pharmacology, toxicology, stability, or compatibility of the combination of bisacodyl and DSS from the already allowable combination of phenolphthalein and DSS.

You included animal toxicology studies and human clinical trial data that were originally submitted to FDA in 1969 as part of an investigational new drug application (IND) in support of the combination of bisacodyl and DSS. The safety of these ingredients in animals has previously been reviewed (40 FR 12909 and 58 FR 46589). Therefore, this letter addresses only the 9 human studies, 8 of which were clinical studies. Because only a brief synopsis of each study was provided, we contacted you on May 2, 1995 to request additional information. You stated that the original data for these studies could not be located and no other information was available. Thus, your company was unable to provide information that would have enabled us to conduct a more thorough evaluation.

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The Office of OTC Drug Evaluation has reviewed your submission and determined that the data are insufficient to include the combination of bisacodyl and DSS in the final monograph for OTC laxative drug products. We have the following comments concerning your submission:

(1) The Weiss data were not a clinical trial but an early study in 1964 to determine the preferred dose that would be suitable for later clinical trials. It was found that the lower dose combination (bisacodyl 5 milligram (mg) and DSS 100 mg) was preferred by more of the 83 study subjects than the higher dose combination (bisacodyl 7.5 mg and DSS 100 mg) due to less cramping. No other details were available.

Double-Blind, Parallel Studies

(2) The Baer study (1967), conducted in 56 subjects (45 to 85 years old) with constipation and other concurrent illnesses (preferably cardiovascular diseases), compared the safety and efficacy of bisacodyl 5 mg and the combination of bisacodyl 5 mg and DSS 100 mg (bisacodyl/DSS) for relief of constipation. Subjects (28 in each group) were given 1 to 2 tablets of either treatment at bedtime for a total of 4 weeks. The efficacy variables measured were all subjective: global effectiveness (excellent/good/fair/poor) and the number of days that subjects considered themselves as having "adequate" bowel movement. Adequate was not defined in the report. Five subjects from each group dropped out due to abdominal pain or gripping. Therefore, data from only 23 subjects in each group were available for evaluation. The results showed no statistically significant difference between the two treatments.

There were much more cases ($p<0.05$) of adverse drug reactions (ADRs) (gripping and abdominal pain) reported in the bisacodyl group (48 events in 15 subjects) than the combination group (28 events in 14 subjects). The investigator concluded that the combination was slightly better than bisacodyl alone, although the difference did not reach statistical significance.

(3) The Landesman study (1967) was conducted in 199 post-partum subjects (17 to 47 years old) and compared bisacodyl with the bisacodyl/DSS combination for its laxative effects over 4 to 5 days. Treatments were given 12 hours post-partum and lasted an average of 4 days. Results showed no significant difference between the two treatments.

ADRs were mild. Five of the 101 subjects in the bisacodyl group and 4 of the 98 subjects in the combination group experienced slight gripping or abdominal pain. One subject in each group had diarrhea, and the subject in the bisacodyl group discontinued therapy because of the diarrhea. Rescue treatments (milk of

magnesia or soapsuds enema) were comparable in the two groups with 7 subjects in the bisacodyl group and 9 subjects in the combination group using the rescue therapy. The investigator stated that the duration of the study was too short for any benefit of DSS to be shown.

(4) The Dubow study (1967), a 6-week study conducted in 150 subjects (9 to 19 years old, 80% male) with a history of mild to moderate constipation, compared bisacodyl with the bisacodyl/DSS combination for laxative effect. There were 78 subjects in the bisacodyl group and 72 subjects in the combination group. During the first 2 weeks (phase-in period) of the study, no subjects received treatment. Baseline parameters were supposed to be established during this period, but no data were provided in the report. Each subject was then given 1 tablet of either treatment daily for the next 4 weeks. The efficacy parameters measured were similar to the Landesman study, i.e., global assessment and the number of subject days with adequate bowel movements. The report indicates that the combination was "slightly" better than bisacodyl alone, although only the analysis of one subparameter was statistically significant. While no subject reported any adverse event in the bisacodyl group, 15 subjects in the combination group reported 33 ADRs (14 had gripping/abdominal pain and 1 had itching). The report indicated that all reactions were mild and of no consequence.

The Office of OTC Drug Evaluation concludes that crucial data are missing from these studies: placebo-control, subject matching, randomization, inclusion/exclusion criteria, compliance, baseline laxation, dietary influences, activity level of subjects during the studies, concomitant medications, etc. Generally, if any statistical analyses were performed, only a p-value was given without specification of which statistical test was chosen. In addition, all studies used a global-type assessment to measure efficacy; however, most current laxative studies use several objective parameters (such as time to effect, consistency of stool, stool weight, stool water content, median strain during bowel movement, stool frequency per week, etc.) to measure efficacy. In addition, the Landesman study used an end-point of 4 to 5 days, while the other two studies used 4 weeks for the assessment of clinical efficacy. A 4-week endpoint does not correlate with the current directions that OTC laxatives be used for not more than 7 days. In addition, both the Baer and Landesman studies failed to demonstrate a statistical advantage of using the combination over bisacodyl alone. The Dubow study was not consistent, only one subparameter of all analyses was statistically significant. Although there were equivalent ADR profiles in the Baer and Landesman studies, the Dubow study showed that the combination product reportedly had a much higher incidence of side-effects compared to using bisacodyl alone (15 out of 72 versus 0 out of 78). Therefore, these studies do not support the approval of the combination.

Double-Blind, Crossover Studies

(5) The Friedman study (1967) compared bisacodyl with bisacodyl/DSS for laxative effect, each for 4 weeks, in 40 subjects (mean age about 60 years, 70 to 80% female). There was a very high dropout rate (reasons not given) with only 16 subjects (40 percent) completing the entire crossover. Efficacy parameters used were similar to previous studies in which subjects were asked at the end of the study about their general response and the number of days with adequate bowel movements.

For general (global) response, 10 out of 16 subjects (63 percent) reported that they were better on the combination compared to 2 out of 16 subjects (13 percent) on bisacodyl; 4 out of 16 (25 percent) stated that there were no differences. This difference was significant ($p<0.01$, statistical test not listed). However, as for adequacy of response for subject-days, there were no differences between the two groups. In addition to the 16 subjects who completed the crossover, 10 other subjects completed half of the study. Seven took the combination and three took the bisacodyl for 4 weeks.

The investigators tried to re-analyze the data (not planned in the protocol) by adding the partial data of these 10 subjects to the data of the 16 subjects. The data were then re-analyzed as a parallel comparison assuming 23 subjects (16 plus the additional 7) in the combination group and 19 subjects (16 plus the additional 3) in the bisacodyl group. However, this secondary analysis did not alter the reported final outcome.

There was a fairly high incidence of ADRs. Fifteen out of 19 subjects on bisacodyl and 14 out of 23 subjects on the combination experienced abdominal pain and gripping. Two subjects on bisacodyl and one subject on bisacodyl/DSS dropped out due to these reactions. Five subjects on bisacodyl and six subjects on bisacodyl/DSS experienced other reactions such as diarrhea, gas pain, heartburn, nausea, headache, itching, diarrhea, etc.

(6) The Goldfarb study (1967), conducted in 30 subjects (mean age 75 years, 14 men and 16 women) with moderate to severe constipation, compared bisacodyl and bisacodyl/DSS for laxative effect, each for 4 weeks. There were two bisacodyl dropouts within 1 week because of diarrhea. An additional subject in the combination group was excluded because the subject took additional bisacodyl. However, by the time of dropout or exclusion, these subjects had completed most of the studies so their global responses were still recorded. Results showed that there were either no differences or that bisacodyl was better than the combination. Subjects were allowed to use any rescue laxative (another product) if constipation was not relieved by the study medications. Cascara, oral and rectal sodium

phosphate, soapsuds enema, mineral oil, milk of magnesia, and suppositories (type not stated) were used for rescue therapy. Many subjects used rescue therapy. Nineteen subjects in the bisacodyl group reported 105 uses of rescue laxative compared to 21 subjects in the combination group who reported 127 uses of rescue laxative during the study. Two subjects in the bisacodyl group also required catherization. The investigators also attempted to do additional preference analysis on the two treatments. Slightly more subjects preferred bisacodyl over the combination; however, this was reported not to be statistically significant.

Many ADRs were reported in the bisacodyl group (39 events by 21 subjects) and the combination group (19 events by 10 subjects). Reported ADRs were gripping, abdominal pain, diarrhea, nausea and vomiting, gas pain, mucous in stool, and malodorous urine.

(7) The Puls study (1967), conducted in 30 subjects (18 to 96 years old, 13 men and 17 women), compared bisacodyl with bisacodyl/DSS for laxative effect, each over 28 days. All subjects had chronic constipation with some other chronic medical condition(s) such as heart or lung disease, cancer, etc. Only 24 subjects completed the crossover. Six subjects were dropouts: one due to no response, one due to side effects on both treatments, and four due to side effects on the combination product. Eight subjects on bisacodyl and nine subjects on the combination required rescue treatment with other laxatives. More ADRs were reported in the bisacodyl group (37 events by 4 subjects) than in the combination group (17 events by 5 subjects). The ADRs were gripping, abdominal pain, nausea, and loose stool.

Although, the analyses of the two primary efficacy variables were not significant, the investigators stated that of the 24 subjects that completed the crossover, 16 stated they did well on either treatment. Of the remaining 8 subjects, 7 stated they were better on the combination ($p=0.035$, by Sign test). Thus, the investigators concluded that the combination was better than bisacodyl.

The Office of OTC Drug Evaluation concludes that these studies (Friedman, Goldfarb, and Puls) are inadequate because they were not well-controlled (i.e., lack randomization, baseline laxation, etc.), contained no specified statistical analyses, and all endpoints were subjective. In addition, for crossover studies, there are additional concerns of carryover effect and treatment-by-period interaction. Further, dropouts were not included in the analyses and no baseline was reported. None of three studies mentioned any washout periods. The results are not convincing and the Friedman study had an extremely high (60 percent) dropout rate. The secondary analysis (to change the data from a crossover design to a parallel comparison) is also invalid. The

high incidence of ADRs in both the Friedman and Goldfarb studies and the liberal use of rescue therapies in the Goldfarb and Puls studies raise serious questions about reliability of the results

In addition, despite the claim of an apparent statistical advantage in some preference analyses in the Friedman and Puls studies, these reports were mainly secondary endpoints with the primary efficacy variables remaining statistically insignificant In fact, based on the global response assessment, the Goldfarb study is a very negative study because 66 to 67 percent of the subjects rated had only poor/fair responses during either treatment and more subjects preferred bisacodyl over the combination.

C. Open-label Studies

(8) The Orchow study (1967), an open-label, three-arm, crossover study conducted in 24 subjects, compared bisacodyl, DSS, and bisacodyl/DSS for laxative effect over 6 weeks. Subjects were chronically debilitated nursing residents with various medical diseases such as paralysis, multiple sclerosis, coronary artery disease, mental problems, etc. About 60 percent of the subjects were over 65 years of age. All subjects were given each treatment for 2 weeks and then switched over to the other treatment. There were no wash-out periods, however, the data on the first day of each treatment were not used to minimize possible carry-over effects. Four subjects dropped out at various times during the treatment; only one was reportedly due to a side-effect (abdominal pain on bisacodyl).

There were more ADRs (abdominal pain or gripping) in the DSS group compared to either the combination or the bisacodyl alone (44 versus 25 versus 24). Diarrhea was occasionally reported (exact number of events not provided) but not significantly different among the three groups. One subject on DSS and on the combination treatment complained about nausea; no subjects on bisacodyl complained.

(9) The Miller study (1967), an open-label, parallel study in 63 postoperative gynecologic subjects (16 to 72 years old), compared senna concentrate (187 mg) and bisacodyl/DSS for laxative effect over 2 to 23 days. Thirty-one subjects were assigned to the senna concentrate group and 32 subjects were assigned to the combination group. On the third day after surgery, 1 to 2 tablets of the combination or senna concentrate were given until the subjects were discharged. The average duration of treatment for the combination was 7.2 days and 6.9 days for senna concentrate. Twelve subjects on the combination and 11 subjects on senna concentrate received concurrent narcotics for pain control. Five subjects on senna concentrate also received soapsuds enema as rescue therapy compared to none on the combination (p=0.02, Fisher's Exact test). Results were

reported to show that the combination was slightly better than senna concentrate but not statistically significant by Chi-square.

More cases of ADRs were reported in the combination group (30 events in 22 subjects) than the senna concentrate group (18 events in 10 subjects). The ADRs were gripping, abdominal pain, nausea, loose stool, diarrhea, urinary retention, headache, dizziness, vertigo, and chills. Five subjects in the combination group and 4 subjects in the senna concentrate group dropped out due to ADRs.

The Office of OTC Drug Evaluation concludes that these studies (Orchow and Miller) have the same problems as the other studies discussed above. In addition, because these studies are unblinded, the usefulness of any subjective efficacy parameters (global and adequacy of bowel movement) is even more questionable. The Orchow study was a crossover study without a washout period. The sample size was relatively small, only 24 subjects, and there was a high dropout rate of 17 percent. The Miller study showed a worse ADR profile for the combination product (22 out of 32 subjects) compared to senna concentrate (10 out of 31 subjects).

The submitted studies do not meet acceptable standards for documenting the safety and efficacy of the bisacodyl/DSS combination for OTC laxative use. The studies were not placebo-controlled, and no details were provided regarding subject matching, randomization, inclusion/exclusion criteria, compliance, baseline laxation, dietary influences, activity level of subjects during studies, concomitant medications, predefined statistical analyses, etc. None of these studies evaluated the efficacy of the individual ingredients versus combination versus placebo. Only one study (Dubow) was said to have measured baseline laxation (results were not reported), and liberal use of rescue laxatives was frequently allowed without adjustment of results for this situation. Two studies were unblinded (Orchow and Miller), results of the blinded crossover studies contradicted each other (Puls and Goldfarb), two parallel, blinded studies showed no difference (Baer and Landesman), and the Weiss study was not set up to evaluate efficacy.

In addition, all the studies submitted used only a subjective assessment for efficacy. Most current laxative studies also use objective parameters (such as consistency of stool, stool weight stool water content, median strain during bowel movement, stool frequency per week, time to effect, etc.) to assess efficacy. The labeled 7-day directions for OTC use and lack of such a predetermined endpoint in these studies is also of concern.

The Office of OTC Drug Evaluation intends to recommend to the Commissioner that the agency respond to your comments in the

above manner in the final monograph for OTC laxative drug products. If you wish to conduct a new study, we suggest that you submit a protocol addressing the above items before starting the study. It should be submitted in three copies, identified with the docket and comment numbers shown at the beginning of this letter, to the Dockets Management Branch (HFD-305), Food and Drug Administration, Room 1-23, 12420 Parklawn Drive, Rockville, MD 20857.

We hope this information will be helpful

Sincerely yours,

William E. Gilbertson, Pharm.D.
Director
Monograph Review Staff
Office of OTC Drug Evaluation
Center for Drug Evaluation and Research

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